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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Petros Tsipouras

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10/30/2006

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EXAMINER

CLOW, LORI A

ART UNIT

PAPER NUMBER

1631

DATE MAILED: 10/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/091,360	TSIPOURAS ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Lori A. Clow, Ph.D.	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 5 September 2006.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 13-18, 40, 41 and 44-46 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 13-18, 40, 41, and 44-46 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### DETAILED ACTION

Applicants' response, filed 9 August 2006, has been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 13-18, 40, 41, and 44-46 are currently pending. Claims 1-12, 19-39, 42, and 43 have been cancelled. Claims 44-46 are newly added.

#### **Claim Rejections - 35 USC § 101**

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 46 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 46 is directed to "the computer-controlled method for rare cell image identification, wherein the x-y-coordinates are a planar coordination component..."

The method step of claim 46 neither results in a physical transformation of matter, **nor** produces a result that is concrete, tangible and useful, as required by 35 USC 101. The claims recite a computer-controlled method for rare cell identification wherein x-y-coordinates are a planar coordination component and the x-z- coordinates are a height/depth coordination component, the components serving to locate rare color images and blobs. The method does not result in a physical transformation of matter. As set forth in the Guidelines for Patent Eligible Subject Matter published November 22, 2005 (1300 OG 142, Annex IV), a method which does

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not result in a physical transformation of matter may be statutory where it recites a concrete, tangible and useful result. While claim 46 does provide a concrete result; i.e. rare cell image identification, the claim is still non-statutory, as it does not provide the result in a tangible form, for example, to a user, and is merely a result that could reside *in silico*.

### **Claim Rejections - 35 USC § 112-New Matter**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-18, 40, 41, and 44-46 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.*

Newly added independent claim 44 recites “precisely locating a rare cell candidate in said blob and continuously recording x, y, and z-coordinates thereof with a computer controlled mobile microscope system searching said optical field starting from an initial position on an optical field of said monolayer”. Applicant has not pointed to support for this newly added limitation, nor is support apparent in the instant specification or the originally filed claims. The specification provides for “recording a physical location” via a “computer controlled x-y mechanical stage” in which “the image provided by the camera is digitized” (page 12, lines 5-8; lines 22-28). The specification further provides for a motorized X-Y stage at page 21, lines 1-9.

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At page 23, the specification discloses that the x-y position of the stage at the starting point is recorded (line 9) and that the z-y position is stored in a database (lines 27 and 28). However, the specification fails to disclose the limitation present in instant step (iii) of claim 44 and therefore is deemed NEW MATTER.

Claims 44, and dependent claims 14, and 15 recite “enhancing detection of said rare cell color image by applying different computer implemented HLS signal masks with selectively limiting pixel value”. Applicant has not provided support for such a limitation nor is support apparent in the instant specification or claims as originally filed. The originally filed claims contained limitations drawn to “creating a cell mask signal representing cell areas in an image” (see original claim 9). The specification provides no support for “enhancing the detection of a rare cell color image” and therefore the limitation is deemed NEW MATTER.

Claim 44 recites, “”automatically locating by a selective tag dispensing system”. Applicant has not provided support for such a limitation nor is support apparent in the instant specification or claims as originally filed. The specification discloses a “device for dispensing reagents” on page 28, however, there is no disclosure of a selective tag dispensing system and therefore this limitation is deemed NEW MATTER.

Claim 44, recites the broad step of “isolating” a sample. Applicant has not provided support for such a limitation nor is support apparent in the specification or claims as originally filed. The specification on pages 3 and 5, discloses receiving a sample and creating a smear. However, this is not support for the full scope of “isolating” a sample. Original Fig. 1 also discloses creating smears. Page 4 discloses obtaining and fixing a sample. However, one can “obtain” a sample from a freezer and therefore this does not support the limitation of “isolating.”

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Page 14 discloses that a sample may be partially enriched for fetal cells. Again, partial enrichment may be considered a type of isolation, but is not supportive of the full scope of "isolating." Therefore, the limitation is deemed NEW MATTER.

### **Claim Rejections - 35 USC § 112-Enablement**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-18, 40, 41, and 44-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must be able to receive a color image signal of a rare cell by performing the steps of isolating a sample, fixing said



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sample, and locating a rare cell candidate (steps i–iii of claim 44). For the reasons set forth below, this constitutes undue experimentation.

b) and c) The specification provides examples for detecting fetal cells from blood smears of maternal blood. The method comprises the following steps, as described on page 10:

Two signals are defined, referred to hereinafter as the first signal and the second signal. As used herein, "signal" should be taken in its broadest sense, as a physical manifestation which can be detected and identified, thus carrying information. One simple and useful signal is the light emitted by a **fluorescent dye** selectively bound to a structure of interest. That signal indicates the presence of the structure, which might be difficult to detect absent the fluorescent dye.

Screening 103 is based on the first signal. The first signal, which in this exemplary embodiment indicates cell identity, may be generated by a fluorescent dye bound to an antibody against the hemoglobin t-chain, i.e., embryonal hemoglobin, for example. Alternatively, for example, a metric of each cell's similarity to the characteristic morphology of nucleated erythrocytes, discerned using cell recognition algorithms may serve as the first signal. In yet another example, the **first signal may be a measure of the presence of the characteristic color of fetal hemoglobin after staining with eosin and acid hematoxylin**. It should now be evident that any detectable indicator of the presence of fetal cells may serve as the first signal, subject to certain constraints noted below.

Diagnosing 105 is based on the second signal. The second signal, which in this exemplary embodiment indicates the presence of a particular genetic characteristic being tested for, may be generated, for example, by in situ PCR-amplification or PCR in situ hybridization or FISH. Cells that emit both signals, i.e., the cell is a fetal cell and contains the genetic characteristic being tested for, will be scored. Counts may be maintained of the number and strengths of the first and second signals detected.

Further, the specification teaches that cells are stained using various procedures, as outlined on pages 18 to 19. From this, samples are processed according to the methods of pages 23 to 27, in which the color image is processed from RGB to HLS signals.

The instant claims, however, do not reflect such steps of cell staining or cell tagging such that one of skill in the art would know how to perform the method of isolating a cell sample, fix a cell sample and locate rare cell candidates to produce a color image. Without steps of labeling

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or staining, the generation of a color signal for processing is not possible and the claims are not enabled.

Further, the claims are drawn to fixing a sample comprising rare cells in cell **aggregates** (blobs) in a monolayer. However, the specification indicates the following with respect to said monolayer:

The invention is described in connection with observing "monolayers" of cells. Monolayer has a specific meaning as used herein. It does not require confluence and can involve single cell suspensions. It means simply that the cells are arranged whereby they are not stacked on top of one another, although all of the cells can be separated from one another. Thus, monolayers can be smears of single cell suspensions or can be a thin layer of tissue. Any solid or exfoliative cytology technique can be employed.

However, the claims are not enabled for fixing a sample in cell aggregates into a monolayer. An aggregate, according to Merriam Webster's Collegiate Dictionary (tenth edition; 1999) is "formed by the collection of units or particles into a body, mass, or amount" or a "clustered mass". One of skill in the art would not know how to fix an aggregate such that a monolayer would be formed in order to effectively image a sample to find a rare cell without disassociating the aggregate in order to form a monolayer. Therefore, the claims are not enabled.

d) The invention is drawn to methods of rare cell image identification by color image manipulation. However, the claims are not enabled, as there are no cellular identification labels or stains such that one of skill in the art would be able to generate a color image for processing and identification of a rare cell. Further, one of skill in the art would not know how to form a monolayer from an aggregate, as is instantly claimed.

e) It would have been well known in the art that increasing the sensitivity of microscopically detecting cellular characteristics requires staining or labeling. This is a more effective way than simply evaluating morphology alone. For example, Mesker et al. (Cytometry



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(1994) Vol. 17, pages 209-215; PTO From 1449 document) teaches the detection of rare cell events using image cytometry in which markers are used to stain cells of interest in different colors. Analysis of the cell images, obtained at different wavelengths, result in high contrast to specifically recognize the different markers. Therefore, in order to generate a color image, staining and markers must be used. The instant claims, however, are not enabled for the generation of a color image.

f) and g) The skill of those in the art of cytometry is high. However, absent steps of labeling or staining in the claims, one of skill in the art would not know how to generate or receive a color image signal.

h) The claims are broad because they are drawn to receiving a color image without the appropriate steps in which to generate the image from the cell sample. The skilled practitioner would first turn to the instant specification for guidance to practice such methods. However, the instant specification indicates that labeling, marking, staining are necessary in order to generate such an image. As such, the skilled practitioner would turn to the prior art for such guidance, however, the prior art shows the same. Finally, said practitioner would turn to trial and error experimentation to determine if the claimed method steps would yield a color image. Such represents undue experimentation.

### **Claim Rejections - 35 USC § 112**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claim 13-18, 40, 41, and 44-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 recites “wherein the step of producing a rare cell image mask”. There is insufficient antecedent basis in the claim for this limitation. No such step is in newly added independent claim 44. Clarification is requested.

Claim 14 recites “and applying a thick filter enhancing the selected rare cell signal”. It is unclear if these are two separate steps or if the “applying a thick filter” is a step that “enhances the selected rare cell signal”. Clarification is requested.

Claim 17 recites “acquiring an image of the body fluid or tissue smear”. There is insufficient antecedent basis in the claim for “the....tissue smear”. Claim 44 recites only a tissue. Clarification is requested.

Claim 18 recites “the rare cell data set”. There is insufficient antecedent basis in the claim for “data set”. Clarification is requested.

Claim 40 recites “the digitized color image”. There is insufficient antecedent basis in the claim for this limitation, as no digitized image is present in claim 44. Clarification is requested.

Claim 44 recites “cell aggregates (blobs)”. It is unclear whether these are intended to be the same or if they are different. Are cell aggregates considered “blobs”? Clarification is requested.

Claim 44 recites “(blobs)” in step (i) and in step (iii) recites “said blob”. It is unclear if the blobs of step (i) are the same or different from the “blob” of step (iii), as one is singular and one is plural. Clarification is requested.

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Claim 44 recites "said optical field". There is insufficient antecedent basis in the claim for such a limitation as no "optical field" limitation preceded step (iii). Clarification is requested.

Claim 44, step (viii), recites "automatically locating by a selective tag dispensing system which is programmed to tag selectively said rare cell in situ to determine biological criteria comprising genomic variation, mutation, or chromosomal aberration". The claim step is unclear, as it is grammatically incorrect. Is intended that the step "automatically locates...to determine" or is it intended that the step "automatically locates" and the "tag" determines biological criteria. Clarification is requested.

Claim 45 recites "a sequence of computer directed steps to identify a rare cell image in accordance with claim 44". It is unclear what steps are implemented by a computer that actually isolate a sample. How can a computer or a computer readable medium isolate a sample? Clarification is requested.

Claim 46 recites "the computer-controlled method for rare cell image identification". There is a lack of antecedent basis, as it is unclear what computer-controlled method is intended. Clarification is requested.

Claim 46 is unclear as to it is what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 46 is also rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for

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example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

### **Conclusion**

No claims are allowed.

The prior art rejections under 35 USC 102 and 103 have been withdrawn in view of the amendments to the claims. Specifically, Douglass (97/20198) does not teach the limitation of step (viii) in claim 44.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

### **Inquiries**

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The

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faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The Central Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

October 25, 2006  
Lori A. Clow, Ph.D.  
Art Unit 1631  
*Lori A. Clow*

MARJORIE A. MORAN  
PRIMARY EXAMINER

*Marjorie A. Moran*  
10/26/06